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Health and Environmental Effects Profile for Cresols

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR CRESOLS

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16. ABSTRACT

The Health and Environmental Effects Profile for cresols was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Cresols has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for cresols is 3.6 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for cresols is 100.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1984.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1^* (U.S. EPA, 1980) is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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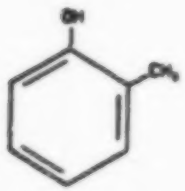
LIST OF ABBREVIATIONS

bw	Body weight
CAS	Chemical Abstracts Service
CNS	Central nervous system
CS	Composite score
DMBA	9,10-dimethyl-1, 2-benzanthracene
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted concentration levels)
LD_{50}	Dose lethal to 50% of recipients
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RNA	Ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RV_d	Dose-rating value
RV_e	Effect-rating value
SCE	Sister chromatid exchange
TLV	Threshold limit value
TWA	Time-weighted average
v/v	Volume per volume
w/v	Weight per volume

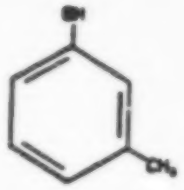
1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Cresols are substituted phenols with the methyl substituent at the o-, m- and p-position relative to the phenolic OH-group. The CAS-Numbers for different isomers of cresols are presented on Table 1-1. The structures of the three isomeric cresols are given below:



o-cresol



m-cresol

p-cresol

Each of the three individual isomers, as well as their mixture, are used commercially. Pure cresol, also known as cresylic acid, is a mixture of three isomers. Commercial cresols contain all three isomers with small amounts of phenols and xylenols (Deichmann and Keplinger, 1981a). Cresylic acids, however, are a commercial mixture of phenolic compounds. An arbitrary standard for cresylic acids prescribes that 50% must boil at >204°C. A typical commercial cut of cresylic acids has the following composition: m- and p-cresol, 0-1%; 2,4- and 2,6-xylenols, 0-3%; 2,3- and 3,5-xylenols, 10-20%; 3,4-xylenol, 20-30%; and C_9-phenols, 50-60% (Hawley, 1981). Therefore, pure and commercial cresol or cresylic acid is different from the commercial mixture called the cresylic acids.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Some of the relevant physicochemical properties, the CAS Registry numbers and the RTECS numbers of the individual isomers and the commercial mixture of cresol or cresylic acid are presented in Table 1-1. These com-

TABLE 1-1

Selected Physical and Chemical Properties of Cresols

Property	Commercial Cresol	o-Cresol	m-Cresol	p-Cresol
Empirical formula	C_7H_8O	C_7H_8O	C_7H_8O	C_7H_8O
Molecular weight	108.13	108.13	108.13	108.13
Synonyms	cresylic acid, cresylol; tricresol	2-methylphenol, o-cresylic acid, o-hydroxy-toluene	3-methylphenol, m-cresylic acid, m-hydroxy-toluene	4-methylphenol, p-cresylic acids, p-hydroxy-toluene
CAS Number	1319-77-3	95-48-7	108-39-4	106-44-5
RTECS Number	GO59500	GO63000	GO61250	GO64750
Appearance and state[a]	colorless, yellow or pinkish liquid	white crystals	colorless to yellowish liquid	crystalline solid
Odor[a]	phenolic	phenolic	phenolic	phenolic
Density at 20/4°C in g/cm^3[b]	1.030-1.038 d_{25}^{25}	1.047	1.034	1.034
Melting point, °C[a]	11-35	30.9	12.0	35.3
Boiling point, °C[a]	191-203	191	203	202
Vapor pressure (mm Hg at 25°C)[c]	NA	0.25	0.15	0.11

TABLE 1-1 (cont.)

Property	Commercial Cresol	o-Cresol	m-Cresol	p-Cresol
Solubility in water, mg/ℓ[d]	NA	31,000 at 40°C	23,500 at 20°C	24,000 at 40°C
-Log acid dissociation constant[e] (pK_a)	NA	10.2	10.0	10.2
Log K_{ow} [f]	NA	1.95	1.99	1.93
Conversion factor at 20°C[d]	1 ppm = 4.50 mg/m^3	1 ppm = 4.50 mg/m^3	1 ppm = 4.50 mg/m^3	1 ppm = 4.50 mg/m^3

[a]Hawley, 1981

[b]Windholz et al., 1983

[c]Deichmann and Keplinger, 1981a

[d]Verschueren, 1983

[e]Morrison and Boyd, 1973

[f]Schultz et al., 1978.

pounds are solid or liquid at room temperature. Both the mixture and the o-isomer tend to become darker with age or upon exposure to light (Windholz et al., 1983). These cresols are soluble in a variety of organic solvents (Windholz et al., 1983).

1.3. PRODUCTION DATA

The three main processes used for the production of cresols are coal tar distillation, petroleum cracking and synthesis from other chemicals (U.S. EPA, 1982). Production by the synthetic routes constitutes more than half of the total United States production of cresols (USITC, 1984). In petroleum refining operations and coal tar distillation, tar acids are distilled to yield mixed cresols. Synthetic cresols are produced by several processes, including methylation of phenol, sulfonation and subsequent hydrolysis of toluene, and oxidation of cumene (U.S. EPA, 1982). The total United States production of cresols (excluding coke oven and gas retort oven) in 1983 was 126.6 million pounds (USITC, 1984).

According to USITC (1984), the following United States companies produced cresols in 1983:

m-cresol

Coppers Co., Inc., Oil City, PA

Merichem Co., Houston, TX

No data regarding United States production volume for m-cresol are available. The TSCA inventory (U.S. EPA, 1982) listed several companies that produced between 3.3 and 32.0 million pounds of this chemical in 1977.

o-cresol

Conoco, Inc., Ponca City, OK

Diamond Shamrock Corp., Tuscaloosa, AL

Ferro Corp., Santa Fe Springs, CA

General Electric Co., Selkirk, NY

Merichem Co., Houston, TX

Pitt-Consal Chemical Co., Anacortes, WA

Sherwin-Williams Co., Chicago, IL

In 1983, the total United States production of o-cresol was 42.8 million pounds (USITC, 1984).

p-cresol

Merichem Co., Houston, TX

Sherwin-Williams Co., Chicago, IL

Also, SRI (1984) lists Bell Flavor and Fragrances, Inc., Northbrook, IL, and Oakland, NJ, as manufacturers of p-cresol in the United States. Recent data on the United States production volume of this chemical are unavailable. The TSCA Inventory (U.S. EPA, 1982) listed several United States companies that produced between 11.2 and 62.1 million pounds of this chemical in 1977.

mixed m- and p-cresols

Koppers Co., Inc., Oil City, PA

Diamond Shamrock Corp., Tuscaloosa, AL

Ferro Corp., Sante Fe Springs, CA

Merichem Co., Houston, TX

Northwest Petroleum Corp., Anacortes, WA

In 1983, the total United States production of mixed m- and p-cresol was 25.0 million pounds (USITC, 1984).

mixed o-, m-, and p-cresol

Koppers Co., Inc., Oil City, PA

Ferro Corp., Sante Fe Springs, CA

Merichem Co., Houston, TX

Diamond Shamrock Co., Tuscaloosa, AL

Pitt-Consal Chemical Co., Anacortes, WA

The United States production volume for the mixed isomers of cresol in recent years is not available. According to TSCA Production Inventory, between 0.01 and 0.11 million pounds of mixed cresols were produced in the United States in 1977 (U.S. EPA, 1982).

1.4. USE DATA

Cresols are consumed directly in many applications as solvents and disinfectants, or they are used as intermediates in the manufacture of other chemicals. The recent use pattern and the percent of total cresols used in each category are given below (CMR, 1984):

Use	Percent of Total
antioxidants	20
wire enamel solvents	15
resins	15
phosphate esters	10
agricultural chemicals	15
export	15
others including cleaning compounds, ore flotation and paint stripping	10

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

The fate of cresols in natural aquatic media with respect to their chemical and photochemical reactions have not been studied comprehensively. The possibility of direct photolysis of p-cresol in aquatic media was studied by Smith et al. (1978). At a p-cresol concentration of ~1 mg/ℓ in distilled water, the half-life of p-cresol exposed to 8 hours of natural sunlight/day was estimated to be 70 days. The photodegradation rate accelerated by a factor of 12 when ~10.0 mg/ℓ of humic acid was present in solution. This acceleration of photolysis of p-cresol was probably due to a photosensitization process caused by humic acid. Similar photosensitization of cresol photolysis in aquatic media with various dyes was also observed by Seeley and Hart (1977).

The photolysis half-life of p-cresol in natural bodies of water having lower light absorption capabilities than distilled water is expected to be >70 days. It has been estimated that half-lives of p-cresol may vary from ~100 days in oligotrophic lakes to >400 days in eutrophic lakes and ponds (Smith et al., 1978). Although photolysis studies for the two other isomeric cresols are not available, their photolytic half-lives are expected to be similar to the photolytic half-life of p-cresol. Therefore, with the exception of the disappearance of cresols from oligotrophic lakes, photolysis may not be a significant fate-determining step.

Cresols do not contain any functional groups that are hydrolyzable. Therefore, hydrolysis of these compounds in aquatic media is unlikely.

The rate constant for the oxidation of p-cresol in aquatic media with peroxyradicals ($RO_2\cdot$) was estimated to be 20 $\ell\ mol^{-1}\ sec^{-1}$ (Smith et al., 1978). Assuming that the concentration of $RO_2\cdot$ radicals is

10^{-9} mol·ℓ^{-1} in aquatic media, the half-life of p-cresol toward oxidation is ≈1 year. The presence of humic acid was found to retard the reaction rate of this process (Smith et al., 1978). If the reaction rates with the other two isomeric cresols are assumed to be similar, the oxidation of cresols with peroxy radicals in natural bodies of water also may not be a significant fate-determining process.

Biodegradation of cresols appears to be the fate-determining process for these compounds in aquatic media. Numerous studies regarding the microbial degradation of cresols with isolated and mixed microorganisms are available. Most of the studies indicate that a certain period of adaptation is required by the microorganisms before degradation can proceed. It has been shown that pure cultures including strains of Pseudomonas putida, Trichosporon cutaneum, Pseudomonas alcaligens, Pseudomonas aeruginosa, Alcaligenes eutrophus and Bacillus stearothermophilis, can biodegrade cresols (Buswell, 1975; Hughes et al., 1984; Hopper and Chapman, 1971; Feist and Hegeman, 1969; Omori and Yamada, 1970; Poh and Bayly, 1980; Paris et al., 1982; Gaal and Neujahr, 1979; Hopper and Taylor, 1975; Bayly and Wigmore, 1973; Banerjee et al., 1984). Similarly, cresols were found to biodegrade in aquatic media with mixed microorganisms (such as activated sludge or mixed soil microorganisms) (Masunaga et al., 1983; Torpy et al., 1983; Hashimoto, 1970; Alexander and Lustigman, 1966). More relevant studies employed natural water as the inoculum for the biodegradation of cresols (Bartholomew and Pfaender, 1983; Coutts et al., 1980; Paris et al., 1983; Visser et al., 1977; Van Veld and Spain, 1983; Pitter, 1976; Pfaender and Bartholomew, 1982; Smith et al, 1978). If a mean value for the microbial transformation rate constant of 2.7×10^{-10} ℓ cells^{-1} hr^{-1} (Paris et al., 1983) and a mean microbial population of 5×10^{8} cells ℓ^{-1} (Banerjee et al., 1984) are used, the half-life of p-cresol in rivers and

ponds will be ≈5 hours. This value is comparable with the estimated half-life of 12 hours for p-cresol in rivers, ponds and eutrophic lakes (Smith et al., 1978). Alexander and Lustigman (1966) observed complete degradation of three isomeric cresols in aquatic media with soil misorganisms within 1 day. Coutts et al. (1980) also reported complete degradation of m-cresols within 3 days in natural river water.

Few studies have been conducted that demonstrate the difference in biodegradation rates of the three isomeric cresols in natural water. With activated sludge, Pitter (1976) showed that the rates of biodegradation of o-, m- and p-cresol were almost identical. Alexander and Lustigman (1966) showed that the meta isomers of benzenes were sometimes more resistant to microbial transformation than the o- and p-isomer. In the case of cresols, however, no difference in the biodegradation rates of the three isomeric cresols was observed (Alexander and Lustigman, 1966).

Two factors that may influence the biodegradation rate of cresols in natural aquatic media are the temperature and the quality of the water. In general, freshwater media have the maximum biotransformation rate for cresols, followed by somewhat lower rates for estuarine waters. Rates for marine waters are much lower than for other kinds of water (Bartholomew and Pfaender, 1983). The half-life of p-cresol biodegradation in different estuarine waters varied between 10 and 43 hours (Van Veld and Spain, 1983). The effect of temperature on the biotransformation roles of cresols in aquatic media was demonstrated by Pfaender and Bartholomew (1982) and Bartholomew and Pfaender (1983). A decrease in temperature from 24 to 11°C increased the biotransformation half-life by a factor of >20 (Pfaender and Bartholomew, 1982); however, the rate of biodegradation of cresols in

marine water was so low that the lowering of water temperature would not change the biodegradation rate appreciably (Bartholomew and Pfaender, 1983).

The anaerobic biodegradation of cresols with sewage sludge was studied by several investigators (Godsy et al., 1983; Boyd et al., 1983; Shelton and Tiedje, 1984). A knowledge of the kinetics of such a process is important for predicting the persistence of cresols in contaminated groundwater. It was estimated by Boyd et al. (1983) that the time required for complete disappearance of m- and p-cresol when incubated anaerobically with 10% sewage sludge was 7 and 3 weeks, respectively. The o-cresol, however, was persistent over a period of 8 weeks.

The transport of p-cresol from aquatic media through volatilization and sorption was studied by Smith et al. (1978). From the measured volatilization rate under moderate stirring conditions (oxygen reaeration rate of 3.6 hrs^{-1}), the half-life for evaporation was estimated to be ≈7 days. The oxygen reaeration rate used by Smith et al. (1978), however, is ≈2-3 orders of magnitude higher than exists in representative bodies of water where the values may range from 0.04-0.008 hr^{-1} (Mabey et al., 1981). Therefore, the half-life for cresol evaporation from natural water is probably substantially longer than the 7 days estimated by Smith et al. (1978). Further support for volatilization not being a significant process is evident from the Henry's Constant for all three isomers calculated to be of the order of 10^{-6} atom m^3/mol^{-1} based on vapor pressure and solubility data of Table 1-1 (solubility data not corrected to 25°C).

The sorption of p-cresol by sediments in aquatic media was estimated by Smith et al. (1978) by multi-component modeling analysis. It was estimated that, depending on the nature of the aquatic medium, only between 0.3 and 0.05% of the total p-cresol would remain sorbed in bottom sediment. The

estimated sorption was highest in pond water (0.3%) and lowest (0.05%) in lake water.

It can be concluded from the above discussion that biodegradation is likely to be the fate-determining process for cresols in most aquatic systems. In ponds, rivers and eutrophic lakes, the half-life of biodegradation of cresols may vary from 5-12 hours. In oligotrophic lake water, the biotransformation rate for cresols may be too slow and photoylsis may determine its fate in such bodies of water (Smith et al., 1978).

2.2. AIR

The atmospheric fate of cresols with respect to $NO_3\cdot$, OH·, atomic O and O_3 has also been studied comprehensively. Carter et al. (1981) studied the reaction rates of nitrate radicals ($NO_3\cdot$) with cresols. Nitrate radicals ($NO_3\cdot$) have been shown to be formed in photochemical smog systems from the following reaction: $O_3 + NO_2 \rightarrow NO_3 + O_2$. From the determined rate constants of 12×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}, 7×10^{-12} cm^3 $molecules^{-1}$ sec^{-1}, and 13×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}, for $NO_3\cdot$ reactions with o-, m- and p-cresol, respectively, and the observed concentration of up to 355 ppt of NO_3 in Los Angeles basin after a pollution episode, Carter et al. (1981) estimated the half-life of cresols due to this reaction to be <1 minute.

The rate constants for the OH· radical reactions with the three isomeric cresols were studied by Atkinson et al. (1978, 1979). The rate constants for these reactions were determined to be 34×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}, 48×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}, and 38×10^{-12} cm^3 $molecule^{-1}$ sec^{-1}, for o-, m-, and p-cresol, respectively (Atkinson et al., 1979). If the concentration of OH· radicals in the atmosphere is assumed to be 10^6 molecules cm^{-3}, the half-lives for cresols in the atmosphere would be <6 hours.

The rate contstant for o-cresol reaction with atomic oxygen O(3p) at 28°C was determined to be 0.58×10^{-12} cm^3 $molecules^{-1}$ sec^{-1} (Atkinson and Pitts, 1975). On the assumption that the concentration of O(3p) in the atmosphere is 5×10^4 molecules cm^{-3} (Graedel, 1978), the half-life for this reaction is estimated to be ~275 days. Similarily, on the basis of the rate constant value for the reactions of all three isomeric cresols with O_3 of 6×10^{-19} cm^3 $molecule^{-1}$ sec^{-1} (Atkinson et al., 1978) and the values for the concentration of O_3 in the atmosphere of 1×10^{12} molecules cm^{-3} (Graedel, 1978), the estimated half-life for this reaction is ~13 days.It can be concluded from the above dicussion that removal of cresols from the atmosphere can be achieved by chemical removal process, such as, formatting of radicals with OH- and NO_{3-}.

The removal of cresols from the atmosphere by dissolution into rain droplets, dry deposition and adsorption on aerosols was studied by Cupitt (1980), who estimated that the probability of physical removal of cre- sols from the atmosphere was not high. In any case, such processes would not be significant in determining this atmospheric fate.

2.3. SOIL

Comprehensive studies demonstrating the removal of cresols through chemical reactions in soil are not available. Considering the photochemical reaction rates of cresols in aquatic media (see Section 2.2.), it would appear to be unlikely that cresols would be significantly removed from soils through photoreaction.

From the biodegradation studies discussed in Section 2.2., it can be determined that biodegradation will probably be the fate-determining process for cresols in soils. Although no definite biodegradation half-lives for cresols in soils were available, the biodegradation half-lives would probably be comparable, or even shorter than in aquatic media since the microbial

population in moist soils would probably be higher than in aquatic media. The degradation rates of cresols in soil may decrease at lower temperature (-2 to 5°C) (Medvedev and Davydov, 1972).

Although no experimental data on the probability of volatility of cresols from soil are available, it can be predicted from its water volatility (see Section 2.2) data that these compounds are not likely to significantly volatilize from soil. From both the reasonably high aqueous solubilities (see Table 1-1) and the low K_{oc} (22-35) (Boyd, 1982), it can be predicted that cresols will leach from soil; however, the rapid biodegradation of cresols in soil may prevent these chemicals from reaching the underground water table. In cases where depletion of the microbial population occurs, which is due to toxic effects of high concentratons of cresols in soil these chemicals may reach groundwater through leaching of soil. Such leaching of cresols from landfills or dump sites and underground coal gasification sites to groundwater have been observed (Sawhney and Kozloski, 1984; Dunlap et al., 1976; Stuermer et al., 1982; McCreary et al., 1983).

3. EXPOSURE

3.1. WATER

Sheldon and Hites (1979) detected cresols at a concentration of 50 ppb in the effluent wastewater of a chemical plant near Philadelphia, PA, but the individual isomers were not separated. After treatment at a sewage treatment plant in Philadelphia, this wastewater still contained cresols at a concentration of 20 ppb; however, no cresols were detected when the effluent from the treatment plant was discharged into the Delaware River near Philadelphia. Jungclaus et al. (1978) reported the detection of cresols (isomer unidentified) in the wastewater from a specialty chemicals manufacturing plant at a concentration of 70-150 ppb. Cresols were also detected at a concentration of 1-10 ppb in the receiving river water of the chemical plant. Ellis et al. (1982) reported the presence of cresol (isomers unidentified) in the effluents from four Publicly-Owned Treatment Works in Illinois, but no quantitative value for these concentrations was provided. Tomson et al. (1981) reported a concentration of ≈0.08 ppb of m- or p-cresol (not separated) in the influent water of an experimental sewage treatment plant in Phoenix, AZ. Hawthorne and Sievers (1984) detected as high as 2.1 mg/ℓ (2100 ppb) of o-cresol and 1.2 mg/ℓ (1200 ppb) m- and p-cresol (not separated) in the wastewater from a shale oil plant. The concentration of p-cresol in a river in Japan, polluted by effluents from the leather industry, was reported to be as high as 204 ppb (Yasuhara et al., 1981). The U.S. EPA STORET Data Base contains 18 entries for o-, m- and p-cresol concentrations in wastewater and surface waters in the United States. The concentration of cresols in each of these entries was ≤25 ppb.

Cresols have also been detected in treated coke oven aqueous condensates, wastewater from petroleum refineries, wastewater from wood preserving

plants, and aqueous effluents from the processing of synfuels (U.S. EPA, 1982). In one instance, sewage water collected downstream from a petroleum refinery contained 415 mg/ℓ (415,000 ppb), 452 mg/ℓ (452,000 ppb) and 484 mg/ℓ (454,000 ppb) of o-, m- and p-cresol, respectively (U.S. EPA, 1982). From the actual effluent discharge data from an o- and p-cresol manu- facturing plant, two different computerized exposure models (EXAMS and ENPART) were used to assess the concentration of these chemicals at different mixing zones of a simulated river system at a maximum loading of ~1 mg/ℓ (1000 ppb). The concentrations were estimated to be 0.64 mg/ℓ (640 ppb) 5 miles downstream and 0.06 mg/ℓ (60 ppb) 30 miles downstream of the river (U.S. EPA, 1982).

Cresols have also been detected in groundwater near landfill dump sites (Dunlap et al., 1976; Sawhney and Kozloski, 1984; McCreary et al., 1983). In a well near a former pine-tar manufacturing site in Gainesville, FL, the concentration of o-cresol and m- and p-cresol (not separated) were determined to be as high as 5.2 (5200 ppb) and 11.1 mg/ℓ (11,100 ppb), respectively (McCreary et al., 1983). Stuermer et al. (1982) reported maximum concentrations o-cresol and m- and p-cresol (unseparated) as 6.6 (6600 ppb) and 16.0 mg/ℓ (16,000 ppb), respectively, in a well near an underground coal gasification site in Northeastern Wyoming.

There are no reliable data on the level of cresols in United States drinking water; therefore, it is not possible to determine human exposure to cresols from this source.

3.2. FOOD

Cresols have been found in foods. p-Cresol has been used as a synthetic flavoring substance in certain foods, although its usage has been regulated as a food additive by the FDA. All three isomeric cresols have been approved by the FDA for use in resinous and polymeric coatings on containers

that come into contact with food (U.S. EPA, 1982); however, no data on the level of cresols in any food could be found.

3.3. INHALATION

The various anthropogenic sources of atmospheric cresols are production related release; inadvertent production and release (e.g., automobile emission, coke oven emissions, petroleum refineries and synfuel production); and release from use of products. Approximately 3.5 million pounds of cresols have been reported to be released to the atmosphere each year, primarily from their use as wire enamel solvents (U.S. EPA, 1982); however, data on the atmospheric level of cresols are sparse. Hoshika and Muto (1978) determined a level of 40 ppb for o-cresol in the ambient air near a phenolic resin factory in Japan. The same study determined the average concentration level of mixed phenols in urban air in Japan to be 440 ppb. In the United States, only one study determined the level of o-cresol in the ambient air near a few production facilities, and determined a median concentration of 1.44 ppt (Brodzinsky and Singh, 1982). In the same study, o-cresol was not detected in the air in Grand Canyon, AZ (detection limit not specified). No measured values for the atmospheric concentrations of m- and p-cresol were located in the literature. Therefore, in spite of the available information that the most likely routes for human exposure of cresols are inhalation and dermal absorption (U.S. EPA, 1982), no estimate on the intake of cresols to the general population that is due to inhalation exposure can be provided. Assuming that an individual inhales 20 m^3 of air/day, the inhalation exposure of o-cresol to populations residing near production facilities will be ~0.13 µg/day.

3.4. DERMAL

Although dermal exposure to cresols during its production and use may be one of the primary human exposure modes, no data regarding dermal exposure were located in the available literature cited in the Appendix. The isomer p-cresol has been used to enhance fragrance in soaps, detergents, lotions and perfume in concentrations averaging 0.005, 0.001, 0.001 and 0.04%, respectively (U.S. EPA, 1982). Most of these uses could result in dermal exposure to p-cresol.

4. PHARMACOKINETICS

4.1. ABSORPTION

The cresols are absorbed across the epithelium of the respiratory and gastrointestinal tracts and through intact skin or open wounds (Deichmann and Keplinger, 1981b). Bray et al. (1950) administered the cresols in $NaHCO_3$ solutions to rabbits by gavage and recovered 65-80% of the doses as free and conjugated cresols in the urine within 24 hours of dosing (Sections 4.3 and 4.4), indicating that at least 65-80% of the dose was absorbed from the gastrointestinal tract. Green (1975) reported a fatal case following dermal exposure of a 12-month-old infant to coal tar fluid (90% cresols in water). No evidence of oral or inhalation exposure was apparent. An autopsy was performed $\geq$4.25 hours after exposure, and cresols were identified in the blood, urine, liver and brain. The blood level was 12 mg/100 mL. Permeability coefficients of the three cresol isomers through epidermal membranes from human abdominal skin have been determined in _in vitro_ experiments (Roberts et al., 1977). Permeability coefficients were estimated from the steady-state slopes of the relation between the cumulative amount of cresol isomer penetrating through a unit area of membrane with time. The following permeability coefficients (k_p) were measured at concentrations of cresol that did not cause damage to the stratum corneum: m-cresol, k_p = 2.54×10^{-4} cm/minute; o-cresol, k_p = 2.62×10^{-4} cm/minute; and p-cresol, k_p = 2.92×10^{-4} cm/minute. For dilute solutions of cresols, the permeability coefficient was a constant over varying concentrations. Once a threshold concentration was reached, the permeability coefficient increased as the cresol concentration increased, indicating that damage to the membrane has occurred. Threshold concentrations resulting in damage were reported as 1.0% w/v for m-cresol, 0.9% w/v for o-cresol and 8.85% w/v for p-cresol.

4.2. DISTRIBUTION

In the previously described case report of fatal dermal exposure to coal tar liquid, cresols were detected in the brain (Green, 1975). In addition, it was stated that all internal organs had a strong cresol odor.

4.3. METABOLISM

Deichmann and Keplinger (1981b) indicated that the metabolism of o-, m- and p-cresols is very similar to the metabolism of phenol. They are oxidized and excreted as sulfate and glucuronate conjugates. Williams (1938) found ≈22% (o- and m-cresol) or 16% (p-cresol) of an orally administered dose to rabbits as a sulfate conjugate in the urine. Bray et al. (1950) found that cresols form conjugates primarily at the hydroxyl group. In rabbits, of the 500 mg of o-cresol administered by gavage, 15% was recovered in the urine as ethereal sulfate and 72% as ether glucuronide. Ten percent of orally administered m-cresol was present as ethereal sulfate and 60% as ether glucuronide. Fifteen percent of orally administered p-cresol at 250-500 mg/rabbit was present as ethereal sulfate and 61% as ether glucuronide. The proportion of the conjugates, however, will vary at different doses. A minor metabolite detected after administration of o- or m-cresol was conjugated dihydroxy toluene. After p-cresol administration, free and conjugated hydroxybenzoic acid were detected.

4.4. EXCRETION

As suggested by the data presented in Section 4.3, the major route of excretion of cresols is in the urine. Bray et al. (1950) found that 80% of the o-cresol, 84% of the m-cresol and 65% of the p-cresol administered to rabbits by gavage was recovered in the urine within 24 hours of dosing. Deichmann and Keplinger (1981b) reported that cresols can also be excreted in bile and exhaled air.

5. EFFECTS

5.1. CARCINOGENICITY

The only studies on the carcinogenicity of cresols encountered in the available literature are tumor promotion assays performed by Boutwell and Bosch (1959), Kaiser (1967), Bock et al. (1971) and case reports of cancer in humans (Garrett, 1975; Wodyka, 1964). Twenty-five microliters of 0.3% DMBA in acetone was applied to shaved dorsal skin areas of female Sutter mice (27-29/group; 2.3 months of age) (Boutwell and Bosch, 1959). This was followed 1 week later by the twice weekly application of one of the cresol isomers (25 µl of a 20% v/v solution in benzene) for 12 weeks. Many of the cresol-treated mice died, presumably from toxic effects of the cresols. Of the animals treated with o-cresol, 59% of the 17 survivors (27 animals originally in the group) developed papillomas. Fifty percent of the 14 survivors treated with m-cresol (29 originally) developed papillomas. Papillomas were observed in 35% of the 20 survivors treated with p-cresol (28 originally). All of the 12 control animals (benzene only following initiation with DMBA) survived to the end of the experiment. No papillomas were observed in the controls; no carcinomas were observed in experimental or control groups.

In a study on the cancer-promoting effects of tea, Kaiser (1967) found that 6 of 15 young Swiss mice developed epithelial-cell carcinomas following treatments consisting of one dermal application of 3,4-benzopyrene (1% in acetone) followed by 55 dermal applications (on alternate days) of brewed tea. The other 9 mice in this group developed precarcinogenic or carcinogenic stages of squamous-cell tumors. A second group of 15 mice that received only one treatment of 3,4-benzopyrene were not observed to develop any pathologic lesions. The authors suggested that the primary cancer-promoting agents in teas are compounds in the phenolic fraction, which

include o-, m- and p-cresol, dimethylphenols and phenol in unspecified concentrations. Bock et al. (1971) demonstrated the promoting activity of cigarette smoke condensate, which is also known to contain cresols. These studies are of limited value in determining the tumor-promoting activity of cresols, since tea and cigarette smoke condensate contain other phenolic compounds.

In a preliminary risk assessment on cresols by the Carcinogen Assessment Group, Albert (1979) reviewed reports by Garrett (1975) and Wodyka (1964) of three cases of cancer in humans exposed to cresols. Two cases of transitional cell sarcoma of the bladder were found in workers occupationally exposed to cresol or creosote (Garrett, 1975). A case of squamous cell carcinoma of the vocal cords was found in a petroleum refinery worker (Wodyka, 1964) who had been exposed to cresol, dichloroethane and chromic acid for several decades.

5.2. MUTAGENICITY

Available data regarding the mutagenicity and genotoxicity of cresols are summarized in Table 5-1. Cresols have not been found to be mutagenic in bacterial assays utilizing Salmonella typhimurium with or without activation (Pool and Lin, 1982; Florin et al., 1980; Douglas et al., 1980; Case Western Reserve, 1980; Crowley and Margard, 1978; Litton Bionetics, 1980a, 1981a; Haworth et al., 1983). Unpublished data (Litton Bionetics, 1980b, 1981b) indicate that a mixture of the three isomers was mutagenic in the mouse lymphoma forward mutation assay with biological activation, while o-cresol in the same assay was not mutagenic.

In vivo and in vitro SCE studies have been conducted on each of the three isomers individually (Cheng and Kligerman, 1984). o-Cresol produced significant increases in SCE when applied in vitro to human diploid fibro-

TABLE 5-1

Mutagenicity and Genotoxicity of Cresols

Assay	Indicator/ Organism	Compound and/ or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	Salmonella typhimurium TA1535 TA1537 TA1538 TA98 TA100	each isomer was tested individually, o-, m- and p-cresol	plate incorporation	0, 0.5, 5, 50, 500, 5000 µg/plate	± S9 from Aroclor-induced rats	-/-	Negative in all strains with or without S9. o-Cresol run not tested at 0.5 µg/plate. The cresols were toxic at 5000 µg/plate	Pool and Lin, 1982
Reverse mutation	S. typhimurium TA98	each isomer was tested individually	plate incorporation	0.03, 0.3, 3, 30 µmol/plate	± S9 from Aroclor-induced rats	-/-	Toxic at 30 µmol/plate	Florin et al., 1980
Reverse mutation	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	each isomer was tested individually	plate incorporation	o-cresol-2.5µl/plate m-cresol-2 mg/plate p-cresol-1 mg/plate	± S9 from Aroclor-induced rats	-/-	The concentrations were the highest tested due to limited solubility	Douglas et al., 1980
Reverse mutation	S. typhimurium TA1535 TA1537 TA98 TA100	each isomer was tested individually	plate incorporation	half-log intervals from 1-10,000 µg/plate	± S9 from Aroclor-induced rats and from Aroclor-induced hamsters	-/-	Negative in all strains with with and without S9	Case Western Reserve, 1980
Reverse mutation	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	p-cresol	plate incorporation	0.008, 0.04 0.02 or 1 µl/plate	± S9	-/-	Negative in all strains with and without S9	Crowley and Margard, 1978
Reverse mutation	S. typhimurium TA1535 TA1538 TA1537 TA98 TA100	mixture of 3 isomers	plate incorporation	0.005-50 µl/plate	± S9 from Aroclor-induced rats	-/-	Negative at all doses with all strains with or without activation	Litton Bionetics, 1980a

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TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Compound and/ or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Reverse mutation	S. typhimurium TA1535 TA1537 TA98 TA100	each isomer tested individually	plate incorporation	0.0, 3.3, 10.0, 33.0, 100, 330 µg/plate	± S9 from Aroclor induced rats or Aroclor induced hamsters	-/-	Negative in all strains with and without S9 (regardless of source)	Haworth et al., 1983
Reverse mutation	S. typhimurium TA1535 TA1537 TA1538 TA98 TA100	o-cresol	plate incorporation	0.01-50 µL/plate	± S9 from Aroclor-induced rats	-/-	Negative at all doses with all strains with or without activation	Litton Bionetics, 1981a
Forward mutation	mouse lymphoma	mixture of all 3 isomers	cell culture	0.488-750 nL/mL	± S9 from Aroclor-induced rats	+/-	Dose related increases observed in mutation frequency with activation; without activation equivocal results suggestive of weak mutagenic activity were seen.	Litton Bionetics, 1980b
Forward mutation	mouse lymphoma	o-cresol	cell culture	3.91-25 nL/mL	± S9 from Aroclor-induced rats	-/-		Litton Bionetics, 1981b
Sister chromatid exchange	human diploid fibroblasts	o-cresol m-cresol p-cresol	cell culture	0-30 mM	none	+ - -	o-Cresol caused significant ($p<0.05$, Dunnett's test) increases in SCE at 10 mM. Biological significance questionable due to toxicity at this concentration and lack of dose-response. Concentrations of 10 and 30 mM were toxic.	Cheng and Kligerman, 1984
Sister chromatid exchange	mouse DBA/2 bone marrow, alveolar macrophages, regenerating liver	each isomer was tested individaully	in vivo	200 mg/kg for o- and m-cresol, 75 mg/kg for p-cresol	NA	-	NC	Cheng and Kligerman, 1984
Sister chromatid exchange	Chinese hamster ovary cells	mixture of all 3 isomers	cell culture	15.6-200 nL/mL 0.5-100 nL/mL	±S9	+/+	The equimixture was less effective in inducing SCE in the presence of S9 fraction than when used alone.	Litton Bionetics, 1980c

TABLE 5-1 (cont.)

Assay	Indicator/ Organism	Compound and/ or Purity	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Sister chromatid exchange	Chinese hamster ovary cells	o-cresol	cell culture	6.25-100 nl/ml 1.56-800 nl/ml	±S9	+/+	Dose-related increase in SCE at 50 and 75 nl/ml (100 nl/ml could not be scored); dose-related increase in SCE from 400-700 nl/ml (800 nl/ml completely toxic)	Litton Bionetics, 1981c
Unscheduled DNA synthesis	human lung fibroblasts WI-28	p-cresol	cell culture	0.01, 0.08 and 0.8 mg	none	+	NC	Crowley and Margard, 1978
Unscheduled DNA synthesis	rat hepatocyte	mixture of 3 isomers	cell culture	0.5-100 nl/ml	NA	+	The authors considered the tested compound to be weakly active.	Litton Bionetics, 1980e
Unscheduled DNA synthesis	rat hepatocyte	o-cresol	cell culture	0.025-1000nl/ml	NA	-	Toxic at concentrations >50 nl/ml	Litton Bionetics, 1981e
Transformation	BALB/3T3 cells	mixture of 3 isomers	cell culture	0.01-8.0 nl/ml	rat hepatocytes	+	Dose-dependent increase in transformed foci was seen.	Litton Bionetics, 1981d
Transformation	BALB/3T3 cells	o-cresol	cell culture	0.264-169 µg/ml				Litton Bionetics, 1981d
Transformation	C3H10T1/2 mouse fibroblast	p-cresol	cell culture	0.06-6.0 µ/l (presumably/plate but not specifically reported by the authors)	none	-	NC	Crowley and Margard, 1978
Viral induction	SV40-transformed Syrian hamster kidney cells	m-cresol	cell culture	10^{-4} to 10^{-6} ml (presumably/plate but not specifically reported)	none	+	50-600 plaque-forming units/ 10^6 cells exposed	Moore and Cochill, 1983
Chromosome Aberrations	Allium cepa onion root tip	each isomer tested individually	NR	NR	NR	+	m-Cresol induced the most pronounced chromosome aberrations, but o- and p-cresol were also positive.	Dean, 1978

NR - Not reported; NC - no comment

blasts, but lack of a dose response prompted the authors to question the significance of this finding; the other isomers were negative in this test. All three isomers were negative in the in vivo assay employing DBA/2 mice. Unpublished data (Litton Bionetics, 1980c, 1981c) indicate that both a mixture of the three isomers and o-cresol alone are capable of producing SCE in Chinese hamster ovary cells in culture. The activity of the cresols was greater without activation than with it.

In studies on the induction of unscheduled DNA synthesis, Crowley and Margard (1978) found p-cresol to be positive in human lung fibroblasts (WI28) in culture with biological activation. A mixture of the three isomers was marginally active in rat hepatocytes in culture (Litton Bionetics, 1980e). o-Cresol did not appear to be active in primary rat hepatocytes in culture (Litton Bionetics, 1981e).

In a cell transformation assay employing BALB/3T3 cells, a mixture of the three isomers was positive (Litton Bionetics, 1980d). An activating system consisting of concurrent incubation with primary rat hepatocytes was employed. o-Cresol alone was negative in this assay, but no activating system was employed (Litton Bionetics, 1981e). In another cell transformation assay using p-cresol, negative results were obtained with the mouse fibroblast cell line C3H10T1/2 (Crowley and Margard, 1978).

In an assay designed as a screening test for putative carcinogens, infectious virus particles were produced from SV40-transformed weanling Syrian hamster kidney cells following treatment with m-cresol (Moore and Coohill, 1983).

In a review article, Dean (1978) reported that sublethal concentrations of cresols were capable of producing abnormal metaphases and anaphases in onion root tip cells, Allium cepa, undergoing mitosis.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of the three cresol isomers were not located in the available literature as cited in the Appendix.

In a study that attempted to use the inhibitory potency of a variety of lipophilic acids in both bacterial and mammalian cell culture as a predictor of potential teratogenicity, Freese et al. (1979) found that all three cresol isomers caused inhibition of cell duplication in cultures of Bacillus subtilis, HeLa cells (strain R), L-132 (derived from normal human lung cells), WI-38 (a transformed line of human lung fibroblasts), and glial cells, line C (from a rat glial tumor). The authors suggested, based on the pK_as and K_{ow}s of the three cresol isomers and the fact that they exhibit strong inhibitory potencies in mammalian tissue culture, that these compounds would be teratogenic in the likely event that they cross the placental barrier; however, no empirical data were presented.

5.4. OTHER REPRODUCTIVE EFFECTS

The only data located in the available literature concerning other reproductive effects were case reports of cresol-containing products (specifically Lysol) being used as intrauterine douches for the purpose of inducing abortions (Vance, 1945; Presley and Brown, 1956). Presley and Brown (1956) reported on four women, 18-35 years of age, who were hospitalized following this procedure; one of the women died of massive hemolysis, pulmonary oil embolism and phenol poisoning. Vance (1945) provided an autopsy report of another woman who died of pulmonary oil embolism following an attempted abortion with intrauterine Lysol injection. Presley and Brown (1956) reported that all the abortions were incomplete.

5.5. SUBCHRONIC AND CHRONIC TOXICITY

Pertinent data regarding the chronic toxicity of the three cresol isomers by either oral or inhalation exposure were not located on the available literature as cited in the Appendix. Table 5-2 presents a summary of the available data for the subchronic toxicity of the cresols.

o-Cresol was administered in the drinking water at a concentration of 0.3 g/ℓ (300 ppm) to 40 male Wistar rats (average body weight of 231±26 g) (Savolainen, 1979). Rats were decapitated in groups of 10 at 5-week intervals following the beginning of exposure. Glial cells were isolated from 5 animals in each group. The brains of the remaining animals were homogenized. A variety of biochemical determinations including cerebral RNA content, glutathione concentration, acid proteinase activity, NADPH-diaphorase, superoxide dismutase, azoreductase, and 2',3'-cyclic nucleotide 3'-phosphohydrolase activity were performed. In brain homogenates from treated rats, glutathione concentration and azoreducatase activity were significantly decreased ($p<0.05$) after 20 weeks of exposure. The RNA content in the brains of exposed rats was increased with respect to controls at the 4th week ($p<0.05$), but not at subsequent weeks. In glial cells of treated animals, 2',3'-cyclic nucleotide 3'-phosphohydrolase activity was significantly increased ($p<0.001$) after 10 weeks of exposure and acid proteinase activity was increased ($p<0.01$) after 20 weeks.

A preliminary report of an immunotoxicology evaluation of o-cresol in B6C3F1 mice indicated that exposure of animals to varying doses (0-130 mg/kg bw/day) of o-cresol in the drinking water for a 14-day period did not produce any significant difference with respect to controls in any of the parameters considered (CIIT, 1983). No evidence was seen of immunotoxicity or altered host resistance (as measured by hematology values, lymphoid organ

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TABLE 5-2

Subchronic Toxicity of Cresols

Species/ Strain	Number/ Sex	Compound	Route	Dose	Length of Exposure	Effects	Reference
Rat/Wistar	40/M 40/control	o-cresol	oral in drinking water	0.3 g/L	20 wk	changes in some brain biochemical parameters	Savolainen, 1979
Rat/NR	NR/NR	o-cresol	inhalation	9 ± 0.9 mg/m^3	2 mo at 6 hr/ day, 5 days/wk; 2 mo at 4 hr/ /day, 5 days/wk	CNS effects (depression of a conditioned defensive reflex), increased leukocyte count in male rats, increased duration of hexobarbital narcosis	Uzhdavini et al., 1972
Rat/NR	NR/NR (control group used)	tricresol (proportions of isomers not specified)	inhalation	0.05 mg/m^3 0.0052 mg/m^3	3 mo of exposure; regimen not reported	high-dose group exhibited loss weight gain, increased CNS excitability, increased oxygen consumption, histologic changes in lung and liver; low dose was a NOEL	Kurlyandskiy et al., 1975
Mice/B6C3F1	NR/F (8-10 wks old)	o-cresol	oral in drinking water	0, 6.5, 32.5, 65 or 130 mg/kg/day	14 days	no effects noted in hematology or immunopathology parameters or in immune functions studied	CIIT, 1983
Mice/NR	NR/NR	o-cresol	inhalation	50 mg/m^3	1 mo at 2 hr/day, 6 days/week	inactivity, reduced body weight gain, hydropic and dystropic changes in CNS, lungs, myocardium, liver and kidney	Uzhdavini et al., 1972
Guinea pigs/NR	NR/NR	o-cresol	inhalation	9±0.8 mg/m^3	2 mo at 6 hr/ day, 52 wk; 2 2 mo at 4 hr/ day, 5 days/wk	quantity of hemoglobin "changed"; increase in eosinophile, variations in electrocardiogram readings	Uzhdavini et al., 1972

NR = Not reported

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weights and cellularity, and cell or humoral-mediated immune functons) in treated animals throughout the course of the study.

As reported in a translation of a study from the Russian literature, an unspecified number of rats and guinea pigs were exposed to o-cresol vapor (9±0.9 mg/m³) for 4 months (2 months at 6 hours/day, 5 days/week and 2 months at 4 hours/day, 5 days/week) (Uzhdavini et al., 1972). In rats, CNS effects as shown by an accelerated depression of a conditioned defensive reflex were observed. In male rats, the leukocyte count in exposed animals reached ≈22,000/mm³ (controls, ≈14,000/mm³) by the 4th month of exposure. One month after the termination of exposure, the leukocyte count returned to normal values. The osmotic stability of the leukocytes was also affected. Bone marrow smears indicated some changes in the composition of the hematopoietic tissue in rats after 4 months. The leukoid-to-erythroid ratio was 1.3:1 in exposed rats and 2.1:1 in control rats, indicating a change in the content of elements of the erythroid series between groups. Although the difference was reported to be statistically significant, no p value was given. Effects of the experimental treatment on the liver were suggested by the observation that the duration of hexobarbital narcosis was 62±5.2 minutes for exposed rats and 37.4±0.67 minutes for control animals. The authors also stated that exposure to o-cresol vapor slightly decreased the reactivity of the pituary-adrenal system in rats, but no indication was given as to how this was measured.

In guinea pigs, Uzhdavini et al. (1972) reported that the "quantity" of hemoglobin changed during the exposure period, but no further explanation was provided. Electrocardiogram readings in guinea pigs showed a slight reduction in the voltage of the R wave, but no mention was made of when these readings were taken.

Uzhdavini et al. (1972) also exposed an unspecified number of mice to o-cresol vapors at a concentration of 50 mg/m³, 2 hours/day, 6 days/week for 1 month. Clinical signs included periods of inactivity during the first minutes of exposure and decreased body weight gain compared with controls. The ends of the tails were reported to fall off after 18-20 days of exposure, but no explanation was provided. No differences in organ weights were observed. Microscopic examination revealed plethora and dystrophic changes of nerve cells and glial elements in the CNS, hyperemia, edema, hyperplasia, hemorrhages and catarrhal bronchitis in the respiratory tract, dystrophic changes in the myocardium and protein dystrophy in the liver and kidneys.

As reported in a translation of a 3-month inhalation study from the Russian literature (Kurlyandskiy et al., 1975), an unspecified number of rats were continuously exposed to a mixture of cresol isomers (proportion not stated) vapor at two concentrations, 0.05 and 0.0052 mg/m³ (plus a control group). The sexes of the rats were not specified. The parameters measured included weight gain, CNS effects, gas exchange, serum proteins, cardiovascular effects and liver effects; however, the means employed to measure these parameters were not explained. High-dose rats failed to gain weight, had increased excitability, increased oxygen consumption, decreased ganma-globulin content of the serums and unspecified changes in lung and liver tissues. The degree of severity or significance of these changes were not reported. No significant changes were observed in the low-dose group, which led the authors to propose this concentration (0.0052 mg/m³) as the mean daily maximum permissible concentration for the cresol mixture in atmospheric air.

5.6. OTHER RELEVANT INFORMATION

Cresols elicit pathologic effects similar to those observed for phenol including irritation, corrosion, hemorrhages and cytoplasmic destruction of the gastrointestinal tract, kidney tubule damage, nodular pneumonia and hepatocellular necrosis (Deichmann and Keplinger, 1981a).

Deichmann and Witherup (1944) reported oral LD_{50} values for rats of the three cresol isomers (10% solution in olive oil) to be 1.35 g/kg for o-cresol, 1.80 g/kg for m-cresol , d 2.02 g/kg for p-cresol. Deichmann and Keplinger (1981b) reported oral LD_{50} values for rabbits under the same conditions to be 0.8 g/kg for o-cresol and 1.1 g/kg for m- and p-cresol. Uzhdavini et al. (1974) reported values for the oral LD_{50} in mice as 0.344 (0.270-0.436) g o-cresol/kg, 0.828 (0.695-0.985) g m-cresol/kg, and 0.344 (0.266-0.443) g p-cresol/kg, and in rats as 1.47 (1.17-1.83) g o-cresol/kg, 2.01 (1.24-3.20) g m-cresol/kg, and 1.46 (1.26-1.67) g p-cresol/kg. Each of the isomers was administered by gavage as a 10% solution in oil. In a Russian study, the mean lethal concentration in mice of a mixture of o-cresol vapor and aerosol was reported to be 178 mg/m³ (Uzhdavini et al., 1972). Vernot et al. (1977) tested the toxicity by dermal exposure of technical grade cresol and the three cresol isomers in female New Zealand white rabbits. The single skin penetration LD_{50} for technical grade cresol was 2.0 g/kg (range 0.7-5.9); for o-cresol, 0.89 g/kg (0.46-1.69), for m-cresol, 2.83 g/kg (no range given); and for p-cresol, 0.30 g/kg (range 0.13-0.91). Loss from the skin was prevented by a gauze patch under latex rubber film. All four compounds also produced visible skin damage on at least two of six treated rabbits.

Shelley and Raque (1972) reported that the topical applications of laundry ink used to mark experimental mice induced hair depigmentation in these

animals. The component of laundry ink responsible for this effect was determined to be p-cresol (Shelley, 1974). p-Cresol (0.5% in acetone) was applied topically three times/week for 6 weeks to plucked or clipped areas on the backs of female CBA/J agouti mice. An additional 30 C57BL/6J male mice were also treated. p-Cresol was found to induce hair depigmentation in both strains of mice.

p-Cresol (108 mg/kg) in olive oil was administered intraperitoneally to four male ddY mice (8 weeks old) in a study designed to delineate the structural features of alkyl-phenols necessary for producing pulmonary toxicity in mice (Mizutani et al., 1982). Four days after treatment the mice were killed and lung damage was assessed by determining the weight of the lung; examination of the lung for pathology was not performed. No significant changes in lung weight were observed; however, a significant decrease in total body weight (10.6% $\pm$ 1.6; $p<0.001$) was noted.

In a study designed to determine effects of tobacco smoke constituents on biochemical functions, a 1 mM concentration of the individual cresol isomers was found to produce inhibition in noradrenaline-induced respiration in isolated hamster brown fat cells ranging from 49-65% depending on the isomer (Pettersson et al., 1980).

Funaki et al. (1976) determined that the O_2-uptake by slices of rabbit liver, kidney and cerebrum was inhibited by m-cresol in a dose-related manner.

Amoore and Hautala (1983), based on the air odor threshold of m-cresol of 0.00028 ppm (v/v) (0.001 mg/m^3), stated that the odor of m-cresol would be detectable by >90% of distracted persons at the TLV of 5 ppm (22 mg/m^3). Smyth (1956) predicted that, at twice the TLV of 5 ppm, irriation of eye, nose or throat would result. At 10 times the TLV, irritation and possible injury of the lungs was predicted.

Perhaps the only evidence of adverse effects in humans exposed to a known concentration of industrial cresols was a statement by Uzhdavini et al. (1972) who reported nasopharyngeal irritation upon exposure to 6 mg/m^3 of vapors (length of exposure unspecified).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Toxicity tests of o-cresol conducted by Slooff et al. (1983) determined LC_{50} and LC_0 values. Tests were conducted using rainbow trout, Salmo gairdneri, fathead minnows, Pimephales promelas, guppies, Poecilia reticulata, and killifish, Oryzias latipes. The 48-hour LC_{50} values were 13, 34, 38 and 41 mg o-cresol/ℓ and the 48-hour LC_0 values were 3.8, 30, 27, 32 mg o-cresol/ℓ, respectively, for the four fish species. Slooff et al., (1983) also reported a 48-hour LC_{50} of 18 mg o-cresol/ℓ for the golden orfe, Leuciscus idus, but an LC_0 was not determined. Comparatively, Juhnke and Luedemann (1978) reported 48-hour LC_0, LC_{50} and LC_{100} values of 10, 17-19, and 21-26 mg m-cresol/ℓ, respectively, for the golden orfe, L. Idus.

In the amphibians, the clawed toad (Xenopus laevis) and the axolotl (Ambystoma mexicanum), Slooff and Baerselman (1980) and Slooff et al. (1983), reported 48-hour LC_{50} values of 38 and 40 mg o-cresol/ℓ and LC_0 values of 24 and 32 mg/ℓ, respectively.

In the freshwater crustacean, Daphnia magna, Canton and Adema (1978) reported 48-hour LC_{50} values ranging from 9.2-23.5 mg o-cresol/ℓ. In the daphnids, D. pulex and D. cucallata, mean 48-hour LC_{50} values were 9.6 and 16.4 mg o-cresol/ℓ, respectively (Canton and Adema, 1978). Bringmann and Kuehn (1977, 1982) reported 24-hour LC_0, LC_{50} and LC_{100} values of 6.3, 19 and 50 mg/ℓ for D. magna exposed to o-cresol. m-Cresol was more toxic, with 24-hour LC_0, LC_{50} and LC_{100} values of 1.6, 8.9 and 25 mg/ℓ, respectively, in D. magna (Bringmann and Kuehn, 1977, 1982). Parkhurst et al. (1979) reported 48-hour LC_{50} values of 18.8 and 1.4 mg/ℓ, respectively, for m-cresol and p-cresol in D. magna.

Emery (1970) reported on the lethal effects of a mixture of cresol isomer on immature and adult stages of the crustaceans, Gammarus fasciatus and Asellus militaris. In both species the molting first instar stage was the most sensitive, having 48-hour LC_{50} values of 7.0 and 21.6 mg cresol/ℓ, respectively. In G. fasciatus, the most sensitive species, 48-hour LC_{50} values were 24.9, 34.3 and 33.9 for adult males, adult females and ovigerous females, respectively. The 48-hour LC_{50} values in A. militaris were 65.4, 68.0 and 61.9 for adult males, adult females and oviferous females, respectively.

McLeese et al. (1979) reported that the marine shrimp, Crangon septemspinosa, survived for ≈59 hours of exposure at 14.2 mg o-cresol/ℓ before lethality occurred. In the marine polychaete, Ophryotrocha diadema, Parker (1984) determined a 48-hour LC_{50} value for cresol (isomer or mixture not specified) between 33 and 100 mg/ℓ.

6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic exposure to any of the cresol isomers or a mixture on aquatic organisms were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Studies by Bringmann and Kuehn (1978) determined toxicity threshold values causing decreased cell multiplication in a blue-green algae, Microcystis aeruginosa, and a green algae, Scenedesmus quadricauda. The threshold values determined after 8 days of incubation were 6.8 and 11.0 mg o-cresol/ℓ and 13.0 and 15.0 mg m-cresol/ℓ, respectively. In the algae, Scenedesmus pannonicus and Chlorella pyrenoidosa, Slooff et al. (1983) reported 48-hour NOEC values for decreased growth of 36 and 34 mg o-cresol/ℓ. The 96-hour NOEC for Selanastrum capricornutum was 65 mg o-cresol/ℓ.

Using mortality, reproduction and dry weight data for the duckweed, Lemma gibba, under static and flow-through conditions, Davis (1981) determined the toxicity of o-cresol. The EC_{50} values determined after 7 days of exposure were 540, 245 and 16.98 mg/ℓ in static tests and 464, 151 and 32.4 mg/ℓ in flow-through tests, respectively, for mortality, reproduction and dry weight.

6.4. RESIDUE

Pertinent data regarding residues of cresols in aquatic organisms or sediments were not located in the available literature as cited in the Appen- dix. p-Cresol has been detected in river water as a result of leather in- dustry effluent (Yasuhara et al., 1981).

6.5. OTHER RELEVANT INFORMATION

The toxicity threshold for growth inhibition in Pseudomonas putida was 33 mg o-cresol/ℓ and 53 mg m-cresol/ℓ (Bringmann and Kuehn, 1980). Levels of p-cresol as low as 1.5 mg/ℓ were toxic to Photobacterium phosphoreum, causing decreased luminescence (Bulich et al., 1981; Ribo and Kaiser, 1983). The yeasts, Pichia sp. and Rhodotorula rubra, had 50% growth reduction following 12 hours of incubation at 400 and 200 mg p-cresol/ℓ, respectively (Kwasniewski and Kaiser, 1983). The toxicity thresholds for decreased cell counts in the protozoan, Entosiphon sulcatum, were 17 mg o-cresol/ℓ and 31 mg m-cresol/ℓ (Bringmann and Kuehn, 1980).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Based in part on the data of Kurlyandskiy et al. (1975) and Uzhdavani et al. (1972) (see Section 5.5.), NIOSH (1978) recommended a TLV-TWA of 10 mg/m³ for all isomers of cresol. ACGIH (1984) and OSHA (Code of Federal Regulations, 1981) adopted a TLV-TWA of 22 mg/m³ (5 ppm). The TLV was recommended by ACGIH (1980) based on analogy to phenol, since the effects, such as corrosion, hemorrhage and necrosis of gastrointestinal tract, kidney tubule damage, nodular pneumonia and necrosis of liver cells are similar.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of any cresol isomer or mixture were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

The cresols were positive as tumor promotors, resulting in the induction of papillomas on the skin of mice following initiation with DMBA (Boutwell and Bosch, 1959). Two cases of transitional cell sarcoma of the bladder (Garrett, 1975) and a case of squamous cell carcinoma of the vocal cords (Wodyka, 1964) have been found in workers occupationally exposed to cresols and other chemicals. No pertinent animal carcinogenicity studies of oral or inhalation exposure to cresols were available, precluding the derivation of a q_1^*. Using the criteria for overall risk assessment evidence of carcinogenicity to human, the three cresols isomers are classified as group 3 chemical by IARC classification and by EPA (1984) proposed guideline for carcinogenicity as group C.

The cresols were negative for reverse mutation with and without metabolic activation in five strains of Salmonella typhimurium but positive in a forward mutation assay in mouse lymphoma cells with activation and in Sister-chromatid exchange assays in a variety of mammalian cell systems (see Table 5-1). Pertinent data regarding the teratogenicity or other reproductive effects of cresols were not located in the available literature as cited in the Appendix.

The available oral toxicity data as discussed in Section 5.5. and summarized in Table 5-2 are insufficient for the derivation of an ADI. In the oral immunotoxicity study using B6C3F1 mice exposed to 6.5-130 mg/kg bw doses of o-cresol in the drinking water for 14 days, no effects were noted in the various assays of immune function, and no hematologic effects were found (CIIT, 1983). Other indices of toxicity were not determined. This study is not suitable for the derivation of an ADI because of its short duration and because it does not establish a NOAEL or NOEL. In a study by Savolainen (1979), Wistar rats were exposed to o-cresol in the drinking

water at 0.3 g/ℓ for 20 weeks. Groups of 10 rats were sacrificed at weeks 5, 10, 15 and 20 after the beginning of exposure. At week 20, significant ($p<0.05$) decreases were noted in glutathione and azoreductase levels in cerebral homogenates and an increase in acid proteinase activity. Systemic pathologic or histologic examination of brain or other tissues was not reported. This study employed only one dose level; therefore, it is not possible to determine whether this dose represents the threshold level for the induction of these effects.

Two subchronic inhalation studies on cresols have been published in the Russian literature. Kurlyandskiy et al. (1975) continuously exposed an unspecified number of rats to mixed cresol isomers at concentrations of 0.005 and 0.05 mg/m³ for 3 months. At the higher exposure level, poorly characterized changes in behavior, serum proteins, lung and liver were reported. No effects were seen at the lower exposure level. No data or measurements for any of the above effects were provided; therefore, it would be inappropriate to use this study for derivation of an ADI.

In an earlier Russian study, Uzhdavini et al. (1972) exposed rats and guinea pigs to o-cresol at a concentration of 9.0 ± 0.9 mg/m³ for 4 months. No effects were seen in guinea pigs. In rats, the authors reported various hematopoietic effects, respiratory tract irritation and sclerosis of lungs. Only one dose was used and no NOAEL or NOEL established.

Uzhdavini et al. (1972) reported that humans exposed to cresol vapors at 6 mg/m³ (length unspecified) experienced nasopharyngeal irritation.

NIOSH (1978) has recommended an occupational exposure criterion of 10 mg/m³ for exposure to cresols. Given the absence of adequate chronic or subchronic data and based on the review of the available literature, the NIOSH criterion would be the most prudent basis for deriving an ADI.

Using the following equation, an ADI of 0.051 mg/kg/day or 3.6 mg/day for a 70 kg man can be derived:

$$ADI = TLV\ (mg/m^3) \times 10\ m^3 \times 5\ days/7\ days \times 0.5\%/70\ kg \times 10$$

where

TLV = 10 mg/m³
10 m³ = human breathing volume during 8-hour day
0.5% = assumed absorption coeffecient
70 kg = assumed body weight of man
10 = uncertainty factor

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The CS values calculated from the data available from experiments reported in Section 5.5 are presented in Table 9-1. The studies in mice by CIIT (1983) and Uzhdavini et al. (1972) are of too short duration for use in estimating the RQ. It was not possible to calculate a human MED from the inhalation study of Kurlyandskiy et al. (1975) in rats because the exposure regimen was not reported.

In the inhalation study by Uzhdavini et al. (1972), rats and guinea pigs were exposed to 9.0±0.9 mg/m³ o-cresol vapor for 6 hours/day, 5 days/week for 2 months and then for 4 hours/day, 5 days/week for an additional 2 months. A variety of effects were observed (reported in detail in Section 5.5.) including a significant change in the content of elements on the erythroid series compared with controls in rats, and unspecified changes in the hemoglobin concentration in guinea pigs. These effects correspond to an RV_e of 4. The other effects observed (changes in susceptibility to hexobarbital and loss of a conditioned reflex in rats, and changes in electrocardiogram readings in guinea pigs) are difficult to interpret but are probably less severe than the bone marrow effects and would therefore be associated with a lower RV_e. Assuming 100% absorption efficiency, the exposure level of 9 mg/m³ can be converted to equivalent dosages for rats and guinea pigs by expanding the exposure from 5 to 24 hours (5 hours is the average of 6 hours and 4 hours/day) and 5 to 7 days/week, by multiplying by the animal daily breathing volume and dividing by the animal body weight. Using a body weight of 0.35 kg and a breathing rate of 0.223 m³/day for rats, the equivalent dosage is 0.85 mg/kg/day. Using a body weight of 0.43 kg and a breathing rate of 0.086 m³/day for guinea pigs the equivalent

TABLE 9-1

Composite Scores for o-Cresols

Species	Route	Concentration	Chronic Human* MED (mg/day)	RV_d	Effects	RV_e	CS	RQ	Reference
Rat/Wistar	oral	0.3 g/l (23.4 mg/kg/day) 20 weeks	28	3.3	changes in brain biochemical parameters	1	3.3	5000	Savolainen, 1979
Rat	inhalation	9.0±0.9 mg/m^3 2 mo at 6 hr/day, 5 days/wk; 2 mo at 4 hr/day, 5 days/wk	1.05	5.5	depression of erythroid series on bone marrow	4	22	100	Uzhdavini et al., 1972
Guinea pig	inhalation	9.0±0.9 mg/m^3 2 mo at 6 hr/day, 5 days/wk; 2 mo at 4 hr/day, 5 days/wk	0.62	5.8	change in "quantity" of hemoglobin	4	23.2	100	Uzhdavini et al., 1972

*The exposure concentrations were divided by an uncertainty factor of 10 to approximate chronic exposure.

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dosage is 0.48 mg/kg/day. Correcting for interspecies extrapolation by multiplying the dosages by the cube root of the ratio of the animal body weight to the average weight of a man (70 kg) the rat and guinea pig dosages are equivalent to human dosages of 0.15 and 0.09 mg/kg/day, respectively, or 10.5 and 6.2 mg/day for a 70 kg man. Dividing the doses by an uncertainty factor of 10 (to approximate chronic exposure) results in MEDs of 1.05 and 0.62 mg/day, respectively, which correspond to RV_ds of 5.5 and 5.8, respectively. The CSs of 22.0 and 23.2 are obtained by multiplying the RV_d by the RV_e and correspond to an RQ of 100 (see Table 9-1).

In the study by Savolainen (1979), the primary effects noted after a 20-week exposure to 0.3 g/ℓ o-cresol in the drinking water of rats were changes in brain biochemical parameters, which correspond to an RV_e of 1. Assuming that rats consume an amount of water/day equivalent to 0.078 times their body weight, this exposure level corresponds to an equivalent dose of 23.4 mg/kg/day. Multiplying the dose by the cube root of the ratio of the body weight of rats to that of humans (assuming that rats weigh 0.35 kg and humans weigh 70.0 kg) and dividing by an uncertainty factor of 10 to approximate chronic exposure results in a human MED of 28 mg/day for a 70 kg man. This corresponds to an RV_d of 3.3. Thus, the CS (RV_dxRV_e) for this study is 3.3, which corresponds to an RQ of 5000.

Since the study of Uzhdavini et al. (1972) results in the highest CS, it is recommended as the basis of the RQ for o-cresol (Table 9-2). The available data are insufficient to determine whether the chronic toxicity of o-cresol is similar to the toxicities of the other isomers or of a mixture of the three isomers; however, the LD_{50} values for the individual isomers (see Section 5.6) are known to be similar. It is thus reasonable to suggest that RQs for m- and p-cresol be based on analogy to o-cresol.

TABLE 9-2

Cresols

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	inhalation
Dose:	0.62 mg/day
Effect:	depression of erythroid series in bone marrow of guinea pigs and rats
Reference:	Uzhdavini et al., 1972
RV_d:	5.8
RV_e:	4
Composite Score:	23.2
RQ:	100

Equivalent human dose

In a previous derivation of the RQ (U.S. EPA, 1983), the inhalation study by Uzhdavini et al. (1972) was also used as the basis; however, different MEDs, RV_ds and CSs were calculated. The differences are due to a difference in the methodology used by U.S. EPA (1983) to calculate the MED from inhalation exposure. In the former methodology, a 50% absorption efficiency was assumed and inhalation exposures were considered to be equivalent among species, such that the human breathing rate was used to calculate the MED directly. In the current methodology, equivalent animal doses are estimated from inhalation exposure and require corrections for interspecies extrapolation using the cube root of the body weight ratios. Nevertheless, the CSs determined by the two methods are virtually identical and both correspond to an RQ of 100.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR (F=1/ED) FOR CARCINOGENICITY

The carcinogenicity data available for the three cresol isomers were summarized in Section 5.1. All three isomers were positive as tumor promotors, inducing papillomas on the skin of mice following initiation with DMBA (Boutwell and Bosch, 1959). Positive results for tumor promotion were also obtained with brewed tea (Kaiser, 1967) and cigarette smoke condensate (Bock et al., 1971) of which cresols are components. Therefore, data for animals are limited. Furthermore, the data are inadequate for the derivation of a potency factor. Two cases of transitional cell sarcoma of the bladder (Garrett, 1975) and one case of squamous cell carcinoma of the vocal cords (Wodyka, 1964) were reported for workers occupationally exposed to cresols and other chemicals; however, the data are not adequate for associating the exposure to tumor induction in humans.

Using the IARC criteria for evaluating the overall weight of evidence of carcinogenicity to humans, the three cresol isomers are most appropriately

classified as Group 3B chemicals (IARC, 1979) and according to EPA (1984) proposed guidelines for carcinogenic risk assessment the weight-of-evidence is judged as Group C meaning there is evidence for carcinogenicity and thus possibly carcinogenic for humans. It should be noted that cresols show positive evidence as a promoter and, therefore, exposure to cresols and other potential carcinogenic agents should be considered with caution.

10. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values for Substances in Workroom Air, 4th ed. with supplements through 1984. Cincinnati, OH. p. 106.

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLVs: Threshold Limit Values for Chemical Substances in the Work Environmental Adopted by ACGIH for 1984-1985. Cincinnati, OH. p. 14.

Albert, R.E. 1979. The Carcinogen Assessment Groups' Preliminary Risk Assessment on Cresols. Type I - Air Program. U.S. EPA.

Alexander, M. and B.K. Lustigman. 1966. Effects of chemical structure on microbial degradation of substituted benzenes. J. Agric. Food Chem. 14: 410-413.

Amoore, J.E. and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3(6): 272-290.

Atkinson, R. and J.N. Pitts, Jr. 1975. Absolute rate constants for the reaction of oxygen (3p) atoms with methoxybenzene and o-cresol. J. Phys. Chem. 79: 541-542.

Atkinson, R., K.R. Darnall and J.N. Pitts, Jr. 1978. Rate constants for the reactions of hydroxyl radicals and ozone with cresols at 300±1° K. J. Phys. Chem. 82(26): 2759-2761.

Atkinson, R., K.R. Darnall, A.C. Lloyd, A.M. Winer and J.N. Pitts, Jr. 1979. Kinetics and mechanisms of the reactions of the hydroxyl radical with organic compounds in the gas phase. Adv. Photochem. 11: 375-488.

Banerjee, S., P.H. Howard, A.M. Rosenberg, A.E. Dombrowski, H. Sikka, D.L. Tullis, 1984. Development of a general kinetic model for biodegradation and its application to chlorophenols and related compounds. Environ. Sci. Technol. 18(6): 416-422.

Bartholomew, G.W. and F.K. Pfaender. 1983. Influence of spatial and temporal variatons on organic pollutant biodegradation rates in an estaurine environment. Appl. Environ. Microbiol. 45(1): 103-109.

Bayly, R.C. and G.J. Wigmore. 1973. Metabolism of phenol and cresols by mutants of Pseudomonas putida. J. Bacteriol. 113(3): 1112-1120.

Bock, F.G., A.P. Swain and R.L. Stedman. 1971. Composition studies on tobacco. XLIV. Tumor-promoting activity of subfractions of the weak acid fraction of cigarette smoke condensate. J. Natl. Cancer Inst. 47: 429-436.

Boutwell, R.K. and D.K. Bosch. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res. 19: 413-424.

Boyd, S.A. 1982. Adsorption of substituted phenols by soil. Soil Sci. 134: 337-343.

Boyd, S.A., D.R. Shelton, D. Berry and J.M. Tiedje. 1983. Anaerobic biodegradation of phenolic compounds in digested sludge. Appl. Environ. Microbiol. 46(1): 50-54.

Bray, H.G., W.V. Thorpe and K. White. 1950. Metabolism of derivatives of toluene. 4. Cresols. Biochem. J. p. 275-278.

Bringmann, G. and R. Kuehn. 1977. Results of the damaging effect of water pollutants on Daphnia magna. Z. Wasser Abwasser Forsch. 10(5): 161-166.

Bringmann, G. and R. Kuehn. 1978. Limiting values for the noxious effects of water pollutant material to blue algae (Microcystis aeruginosa) and green algae (Scenedesmus quadricauda) in cell propagation inhibition tests. Vom Wasser. 50: 45-60.

Bringmann, G. and R. Kuehn. 1980. Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. Water Res. 14(3): 231-241.

Bringmann, G. and R. Kuehn. 1982. Results of toxic action of water pollutants on Daphnia magna Straus tested by an improved standardized procedure. Z. Wasser Abwasser Forsch. 15(1): 1-6.

Brodzinsky, R. and H.B. Singh. 1982. Volatile organic chemicals in the Atmosphere: An Assessment of Available Data. Final Report on Contract 68-02-3452. U.S. EPA, ESRL, ORD, Research Triangle Park, NC.

Bulich, A.A., M.W. Greene and D.L. Isenberg. 1981. Reliability of the bacterial luminescence assay for determination of the toxicity of pure compounds and complex effluents. ASTM Spec. Tech. Publ. 737 (Aquatic. Toxicol. Hazard Assess.), 338-347.

Buswell, J.A. 1975. Metabolism of phenol and cresols by Bacillus stearothermophilus. J. Bacteriol. 124(3): 1077-1083.

Canton, J.H. and D.M.M. Adema. 1978. Reproducibility of short-term and reproduction toxicity experiments with Daphnia magna and comparison of the sensitivity of Daphnia magna with Daphnia pulex and Daphnia cucullata in short-term experiments. Hydrobiologia. 59(2): 135-140.

Carter, W.P.L., A.M. Winer and J.N. Pitts, Jr. 1981. Major atmospheric sink for phenol and the cresols. Reaction with the nitrate. J. Am. Chem. Soc. 15(7): 829-831.

Case Western Reserve. 1980. Unpublished data on experiments performed by Case Western Reserve as part of the Environmental Mutagenesis Test Development Program of the National Toxicology Program. Personal communication from DA Canter, NTP, NIH, to B.K. Means, Office of Pesticides and Toxic Substances.

Cheng, M. and A.O. Kligerman. 1984. Evaluation of the genotoxicity of cresols using sister-chromatid exchange (SCE). Mutat. Res. 137: 51-55.

CIIT (Chemical Industry Institute of Toxicology). 1983. Preliminary result of in vivo and in vitro sister chromatid exchange assays on cresol isomers and of an immunological evaluation of o-cresol. Memorandum to Office of Pesticides and Toxic Substances. CIIT, RTP, NC. CIIT Docket No. 12283.

CMR (Chemical Marketing Reporter). 1984. Chemical Profile: Cresylics. p. 66. November 12, 1984.

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. 29 CFR 1910.1000.

Coutts, R.T., E.E. Hargesheimer and F.M. Pasutto. 1980. Application of a direct aqueous acetylation technique to the gas chromatographic quantitation of nitrophenols and 1-naphthol in environmental water samples. J. Chromatogr. 195(1): 105-112.

Crowley, J.P. and W. Margard. 1978. Summary reports on determination of mutagenic/carcinogenic and cytotoxic potential of four chemical compounds to Sherwin Williams Company. Unpublished data.

Cupitt, L.T. 1980. Fate of Toxic and Hazardous Materials in the Air Environment. U.S. EPA, Atmospheric Chemistry and Physical Division, ESRL, Research Triangle Park, NC. EPA-600/3-80-084. NTIS PB80-221948.

Davis, J.A. 1981. Comparison of static-replacement and flow-through bioassays using duckweed, Lemma gibba G-3. 106 p. Gov. Rep. Announce. Index. 81(18): 3790. EPA-560/6-81-003. NTIS PB81-187650.

Dean, B.J. 1978. Genetic toxicology of benzene, toluene, xylenes and phenols. Mutat. Res. 47(2): 75-97.

Deichmann, W.B. and M.L. Keplinger. 1981a. Industrial toxicology. Phenols and phenolic compounds. In: Patty's Industrial Hygiene and Toxicology. Vol. 2A, 3rd ed., G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., NY.

Deichmann, W.B. and M.L. Keplinger. 1981b. Cresol. In: Patty's Industrial Hygiene and Toxicology, Vol. 2A, 3rd ed. G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 2597-2601.

Deichmann, W.B. and S. Witherup. 1944. Phenol Studies. VI. The acute and comparative toxicity of phenol and o-, m- and p-cresols for experimental animal. J. Pharmacol. Exp. Ther. 80: 233.

Douglas, G.R., E.R. Nestmann, E.R. Betts, et al. 1980. Mutagenic activity in pulp mill effluents. Water Chlorination: Environ. Impact Health Eff. 3: 865-880.

Dunlap, W.J., D.C. Shew, J.M. Robertson and C.R. Toussaint 1976. Organic pollutants contributed to groundwater by a landfill. U.S. EPA, ORD. (Rep.), Gas Leachate Landfills - Form. Collect. Treat. PB-251 161: 96-110. EPA-600/9-76-004

Ellis, D.D., C.M. Jone, R.A. Larson and D.J. Schaeffer. 1982. Organic constituents of mutagenic secondary effluents from wastewater treatment plants. Arch. Environ. Contam. Toxicol. 11(3): 373-382.

Emery, R.M. 1970. Comparative acute toxicity of cresol to two benthic crustaceans. Water Res. 4(7): 485-491.

Feist, C.F. and G.D. Hegeman. 1969. Phenol and benzoate metabolism by Pseudomonas putida; regulation of tangential pathways. J. Bacteriol. 100(2): 869-877.

Florin, I., L. Rutbert, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicol. 15(3): 219-232.

Freese, E., B.C. Levin, R. Pearce, et al. 1979. Correlation between the growth inhibitory effects, partition coefficients and teratogenic effects of lipophilic acids. Teratology. 20(3): 413-439.

Funaki, H., R. Hatsuda, M. Kokado and S. Tsunekazu. 1976. Effects of m-cresol on oxygen-uptakes by tissues (liver, kidney, and cerebrum). Kyoto Furitsu Ikd Daigaku Zasshi. 85(11): 737-740.

Gaal, A. and H.Y. Neujahr. 1979. Metabolism of phenol and resorcinol in Trichosporon cutaneum. J. Bacteriol. 137(1): 13-21.

Garrett, J.S. 1975. Association between bladder tumors and chronic exposure to cresols and creosote (letter). J. Occup. Med. 17: 492. (Cited in Albert, 1979)

Godsy, E.M., D.F. Goerlitz and G.G. Erlich. 1983. Methanogenesis of phenolic compounds by a bacterial consortium from a contaminated aquifer in St. Louis Park, Minnesota. Bull. Environ. Contam. Toxicol. 30(3): 261-268.

Graedel, T.E. 1978. Chemical Compounds in the Atmosphere. Academic Press, NY.

Green, M.A. 1975. A household remedy misused -- fatal cresol poisoning following cutaneous absorption (a case report). Med. Sci. Law. 15(1): 65-66.

Hashimoto, K. 1970. Oxidation of phenols by yeast. I. New oxidation product from p-cresol by an isolated strain of yeast. J. Gen. Appl. Microbiol. 16(1): 1-13.

Hawley, G.G. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold, Co., NY. p. 285.

Haworth, S., T. Lawlor, K. Mortelmans, W. Speck and E. Zeiger. 1983. Salmonella mutagenicity test results for 250 chemicals. Environ. Mutagen. Suppl. 1: 3-142.

Hawthorne, S.B. and R.E. Sievers. 1984. Emission of organic air pollutants from shale oil wastewaters. Environ. Sci. Technol. 18(6): 483-490.

Hopper, D.J. and P.J. Chapman. 1971. Gentisic acid and its 3- and 4-methyl substituted homologs as intermediates in the bacterial degradation of m-cresol, 3,5-xylenol, and 2,5-xylenol. Biochem. J. 122(1): 19-28.

Hopper, D.J. and D.G. Taylor. 1975. Pathways for the degradation of m-cresol and p-cresol by Pseudomonas putida. J. Bacteriol. 122(1): 1-6.

Hoshika, Y. and G. Muto. 1978. Gas-liquid-solid chromatographic determination of phenols in air using Tenax-GC and alkaline precolumns. J. Chromatogr. 157(1): 277-284.

Hughes, E.J.L., R.C. Bayly and R.A. Skurray. 1984. Evidence for isofunctional enzymes in the degradation of phenol, m- and p-toluate, and p-cresol via catechol meta-cleavage pathways in Alcaligines eutrophus. J. Bacteriol. 158(1): 79-83.

IARC (International Agency for Research on Cancer). 1979. In: Chemicals and Industrial Processes Associated with Cancer in Human. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyon, France. Monographs Supplement 1, p. 11.

Juhnke, I. and D. Luedemann. 1978. Results of the study of 200 chemical compounds on acute fish toxicity using the Golden Orfe test. Z. Wasser Abwasser Forsch. 11(5): 161-164.

Jungclaus, G.A., V. Lopez-Avila and R.A. Hites. 1978. Organic compounds in an industrial waste water: A case study of their environmental impact. Environ. Sci. Technol. 12(1): 88-96.

Kaiser, H.E. 1967. Cancer-promoting effects of phenols in tea. Cancer. 20: 614-616.

Kurlyandskiy, B.A., D.P. Partsef and A.R. Chernomorskiy. 1975. Methods for determination of mean daily MPC or trioresol in the atmosphere. Gig. Sanit. 5: 85-87. (Translated from Russian)

Kwasniewski, K and K.L.E. Kaiser. 1983. Toxicities of selected phenols to fermentative and oxidative yeasts. Bull. Environ. Contam. Toxicol. 31(2): 188-194.

Litton Bionetics. 1980a. Mutagenic evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the Ames Salmonella/microsome plate test -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980b. Mutagenic evaluation of ortho-, meta- and para-cresol 33.3% each in the mouse lymphoma forward mutation assay -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980c. Mutagenic evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the sister chromatid exchange assay with Chinese hamster ovary cells -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980d. Evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the primary rat hepatocyte unscheduled DNA assay. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1980e. Evaluation of sample containing 33.3% each of ortho-, meta- and para-cresol in the in vitro transformation of BALB/3T3 cells assay with activation by primary rat hepatocytes -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0780-0079.

Litton Bionetics. 1981a. Mutagenic evaluation of N50C-81-3 [o-cresol] in the Ames Salmonella/microsome plate test -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Litton Bionetics. 1981b. Mutagenic evaluation of N50C-81-3 [o-cresol] in the mouse lymphoma forward mutation assay -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Litton Bionetics. 1981c. Mutagenic evaluation of N50C-81-3 [o-cresol] sister chromatid exchange assay with Chinese hamster ovary cells -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Litton Bionetics. 1981d. Evaluation of N50C-81-3 [o-cresol] in the in vitro transformation of BALB/3T3 cells assay [without activation] -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Litton Bionetics. 1981e. Evaluation of M50C-P1-3 [o-cresol] in the primary rat hepatocyte unscheduled DNA synthesis assay -- Final report. Unpublished data submitted by the Cresol Task Force to the Office of Toxic Substances, U.S. EPA. FYI-OTS-0981-0126.

Mabey, W.R., J.H. Smith, R.T. Podell, et al. 1981. Aquatic Fate Process Data for Organic Priority Pollutants. Monitoring and Data Support Div., Office of Water Regulations and Standards, Washington, DC. EPA 440/4-81-014. p. 428.

Masunaga, S., Y. Urushigawa and Y. Yonezawa. 1983. Microbial transformation of o-cresol to dihydroxytoluenes by phenol acclimated activated sludge. Chemosphere. 12: 1075-1082.

McCreary, J.J., J.G. Jackson and J. Zoltek, Jr. 1983. Toxic chemicals in an abandoned phenolic waste site. Chemosphere. 12(11/12): 1619-1632.

McLeese, D.W., V. Zitko and M.R. Peterson. 1979. Structure-lethality relationships for phenols, anilines and other aromatic compounds in shrimp and clams. Chemosphere. 8(2): 53-57.

Medvedev, V.A. and V.D. Davydov. 1972. Transformation of individual coal-tar-chemical-industry organic products in a chernozem soil. Pochvovedenie. (11): 22-8. (Rus.) (CA 78:706185)

Mizutani, T., I. Ishida, K. Yamamoto and K. Tajima. 1982. Pulmonary toxicity of butylated hydroxytoluene and related alkylphenols: Structural requirements for toxic potency in mice. Toxicol. Appl. Pharmacol. 62(2): 273-281.

Moore, S.P. and T.P. Coohill. 1983. An SV40 mammalian inductest for putative carcinogens. Prog. Nucleic Acid Res. Mol. Biol. 29: 149-153.

Morrison, R.T. and R.N. Boyd. 1973. Organic Chemistry, 3rd ed. Allyn and Bacon, Inc., Boston. p. 787-808.

NIOSH (National Institute for Occupational Safety and Health). 1978. Criteria for a Recommended Standard... Occupational Exposure to Cresol. U.S. DHEW, PHS, CDC, Cincinnati, OH. Publ. No. 78-133.

Omori, T. and K. Yamada. 1970. Utilization of hydrocarbons by microorganisms. XVII. Metabolism of p-xylene and related compounds. Agric. Biol. Chem. 34(5): 664-669.

Paris, D.F., N.L. Wolfe and W.C. Steen. 1982. Structure-activity relationships in microbial transformations of phenols. Appl. Environ. Microbiol. 44(1): 153-158.

Paris, D.F., N.L. Wolfe, W.C. Steen and G.L. Baughman. 1983. Effect of phenol molecular structure on bacterial transformation rate constants in pond and river samples. Appl. Environ. Microbiol. 45(3): 1153-1155.

Parker, J.G. 1984. The effects of selected chemicals and water quality on the marine polychaete Ophryotrocha diadema. Water Res. 18(7): 865-868.

Parkhurst, B.R., A.S. Bradshaw, J.L. Forte and G.P. Wright. 1979. An evaluation of the acute toxicity to aquatic biota of a coal conversion effluent and its major components. Bull. Environ. Contam. Toxicol. 23(3): 349-356.

Pettersson, B., M. Curvall and C.R. Enzell. 1980. Effects of tobacco smoke compounds on the noradrenaline induced oxidative metabolism in isolated brown fat cells. Toxicology. 18(1): 1-15.

Pfaender, F.K. and G.W. Bartholomew. 1982. Measurement of aquatic biodegradation rates by determining heterotrophic uptake of radiolabeled pollutants. Appl. Environ. Microbiol. 44(10: 159-164.

Pitter, P. 1976. Determination of biological degradability of organic substances. Water Res. 10(3): 231-235.

Poh, C.L. and R.C. Bayly. 1980. Evidence for isofunctional enzymes used in m-cresol and 2,5-xylenol degradation via the gentisate pathway in Pseudomonas alcaligenes. J. Bacteriol. 143(1): 59-69.

Pool, B.L. and P.Z. Lin. 1982. Mutagenicity testing in the Salmonella typhimurium assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem. Toxicol. 20(4): 386-391.

Presley, J.A. and W.E. Brown. 1956. Lysol-induced criminal abortion. Obstet. Gynecol. 8: 368-370.

Ribo, J.M. and K.L.E. Kaiser. 1983. Effects of selected chemicals to photoluminescent bacteria and their correlations with acute and sublethal effects on other organisms. Chemosphere. 12(11-12): 1421-1442.

Roberts, M.S., R.A. Anderson and J. Swarbrick. 1977. Permeability of human epidermis to phenolic compound. J. Pharm. Pharmacol. 29(11): 677-683.

Savolainen, H. 1979. Toxic effects of peroral o-cresol intake on rat brain. Res. Commun. Chem. Pathol. Pharmacol. 25(2): 357-364.

Sawhney, B.L. and R.P. Kozloski. 1984. Organic pollutants in leachates from landfill sites. J. Environ. Qual. 13(3): 349-352.

Schultz, T.W., L.N. Kyte and J.N. Dumont. 1978. Structure-toxicity correlations of organic contaminants in aqueous coal-conversion effluents. Arch. Environ. Contam. Toxicol. (1): 457-463.

Seely, G.R. and R.L. Hart. 1977. Preparation of stained alginate beads for photosensitized oxidation of organic pollutants. Environ. Sci. Technol. 11(6): 623-625.

Sheldon, L.S. and R.A. Hites. 1979. Sources and movement of organic chemicals in the Delaware River. Environ. Sci. Technol. 13(5): 574-579.

Shelley, W.B. 1974. p-Cresol. Cause of ink-induced hair depigmentation in mice. Br. J. Dermatol. 90(2): 169-174.

Shelley, W.B. and C.J. Raque. 1972. Delayed pattern hair depigmentation in CBA mice following application of laundry ink. J. Invest. Dermatol. 59: 202-205. (Cited in NIOSH, 1978)

Shelton, D.R. and J.M. Tiedje. 1984. General method for determining anaerobic biodegradation potential. Appl. Environ. Microbiol. 47(4): 850-857.

Slooff, E. and R. Baerselman. 1980. Comparison of the usefulness of the Mexican axolotl (Ambystoma mexicanum) and the clawed toad (Xenopus laevis) in toxicological bioassays. Bull. Environ. Contam. Toxicol. 24(3): 439-443.

Slooff, E., J.H. Canton and J.L.M. Hermens. 1983. Comparison of the susceptibility of 22 freshwater species to 15 chemical compounds. I. Subacute toxicity tests. Aquat. Toxicol. 4(2): 113-128.

Smith, J.H., W.R. Mabey, N. Bohomus, et al. 1978. Environmental Pathways of Selected Chemicals in Freshwater Systems, Part II. Laboratory Studies. U.S. EPA, Athens, GA. EPA-600/7-78-074.

Smyth, H.F. 1956. Improved communication -- Hygienic standards for daily inhalation. Am. Ind. Hyg. Assoc. Quar. 17: 129-185.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers: United States of America. SRI, Menlo Park, CA. p. 509.

Stuermer, D.H., D.J. Ng and C.J. Morris. 1982. Organic contaminants in groundwater near an underground coal gasification site in northeastern Wyoming. Environ. Sci. Technol. 16(9): 582-587.

Tomson, M.B., J. Dauchy, S. Hutchins, C. Curran, C.J. Cook and C.H. Ward. 1981. Groundwater contamination by trace level organics from a rapid infiltration site. Water Res. 15(9): 1109-1116.

Torpy, M.F., R.G. Luthy and L.A. Raphaelian. 1983. Biological oxidation of organic constituents in tar-sand combustion-process water. Biotechnol. Bioenc. 25(12): 3163-3176.

U.S. EPA. 1982. Assessment of testing needs: Cresols support document. Test Rule Development Branch, Assessment Div., Office of Toxic Substances, Office of Pesticides and Toxic Substances, U.S. EPA, Washington, DC.

U.S. EPA. 1983. Reportable Quantity Document for Cresol. External Review Draft. ECAO-CIN-R088. Environmental Criteria and Assessment Office, U.S. EPA, Cincinnati, OH.

U.S. EPA. 1984. Proposed Guidelines for Carcinogenicity Risk Assessment. Federal Regulation. 49(227): 46294-46301.

USITC (U.S. International Trade Commission). 1984. Synthetic Organic Chemicals. United States Production and Sales, 1983. USITC Publ. No. 1588, USITC, Washington, DC. p. 27-55.

Uzhdavini, E.R., N.K. Astafyeve, A.A. Mamyeva and G.Z. Bakhtizina. 1972. Inhalation toxicity of o-cresol. Tr. Urim. Nauchno-Issled Inst. Gig. Profzabol. 7: 115-119. (Translated from Russian)

Uzhdavini, E.R., N.K. Astafyeva and A.A. Mamayeva. 1974. The acute toxicity of lower phenols. Gig. Tr. Prof. Zabol. 18: 58-59. (Rus.) (Cited in NIOSH, 1978)

Vance, B.M. 1945. Intrauterine injection of Lysol as an abortifacient. Report of a fatal case complicated by oil embolism and Lysol poisoning. Arch. Pathol. 40: 395-398.

Van Veld, P.A. and J.C. Spain. 1983. Degradation of selected xenobiotic compounds in three types of aquatic test systems. Chemosphere. 12: 1291-1305.

Vernot, E.H., J.D. MacEwen, C.C. Haun and E.R. Kinkead. 1977. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxicol. Appl. Pharmacol. 42(2): 417-423.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY. p. 403-410.

Visser, S.A., G. Lamontagne, V. Zoulalian and A. Tessier. 1977. Bacteria active in the degradation of phenols in polluted waters of the St. Lawrence River. Arch. Environ. Contam. Toxicol. 6(4): 455-469.

Williams, R.T. 1938. Studies in detoxication. I. The influence of (a) dose and (b) o-, m-, and p-substitution on the sulfate detoxication of phenol in the rabbit. Biochem. J. 32: 877-878.

Windholz, M., S. Budavini, R.F. Blumetti and E.S. Otterbein, Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ. p. 369.

Wodyka, J. 1964. Precancerous states of the larynx. Pol. Tyg. Ted. 19: 91-94. (Cited in Albert, 1979)

Yasuhara, A., H. Shiraishi, M. Tsuji and T. Okuno. 1981. Analysis of organic substances in highly polluted river water by mass spectrometry. Environ. Sci. Technol. 15(5): 570-573.

APPENDIX A

This profile is based on data identified by computerized literature searches of the following:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in December, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1984. TLVs: Threshold Limit Values for Chemical Substances in the Work Environment adopted by ACGIH for 1984-1985. Cincinnati, OH. 116 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd re. ed. Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd re. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816

Clayton, G.D. and F.E. Clayton, Eds. 1982. Patty's Industrial Hygiene and Toxicology, 3rd re. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1985. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Manage- ment Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, I.N. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nos Trand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemi- cal Producers. Menlo Park, CA.

U.S. EPA. 1982. Chemical Activities Status Report. 3rd ed. (EPACASR). Offices of Pesticides and Toxic Substances, Washington, DC. EPA 560/TIIS-82-002b.

U.S. EPA. 1983. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Regis- tration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1984. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Ser. Resource Publ. 137. Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, Second ed. Prepared for the Resources Agency of California. State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.

In addition, the following documents were obtained and received:

Federal Register. 1977. TSCA (Toxic Substances Control Act) interagency testing committee. Initial report to the Administrator, U.S. EPA. Fed. Reg. 42(197): 55026-55080.

U.S. EPA. 1982. Assessment of Testing Needs: Cresols Support Document. Proposed Health Effects Test Rule. Toxic Substances Control Act. Section 4. Test Rule Development Branch, Assessment Division, U.S. EPA, Office of Toxic Substances, Washington, DC.

Federal Register. 1983. Cresols; Proposed Test Rules. U.S. EPA. 48(133) FR 31812-31820.

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